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Abstracts

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ATP analogues and UTP activate phospholipase C (PLC) in bovine glomerular endothelial cells (gEC). *V. Briner and F. Kern, University Hospital Bern, Department of Medicine, Bern, Switzerland.* Purine and pyrimidine nucleotides are produced in blood, vessels and kidney and may induce both vasoconstriction and vasodilation, thus modulating glomerular filtration rate (GFR). In glomerular mesangial cells (gMC), ATP and UTP stimulate phosphoinositol turnover and induce contraction. The present study investigates the effects of nucleotides on inositol-1,4,5-trisphosphate (IP_3) and IP_1 generation and cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) and the receptors involved in signal transduction. The purine nucleotides ATP, [β,γ-imido]-ATP, ADP and the pyrimidine UTP induced a dose dependent rise in $[Ca^{2+}]_i$. A dose of 10^{-3} M of these nucleotides stimulated peak rise in $[Ca^{2+}]_i$ from a basal concentration of 93 ± 2 nmol/liter to 533 ± 23 nmol/liter by ATP; to 441 ± 39 nmol/liter by [β,γ-imido]-ATP; to 460 ± 31 nmol/liter by ADP; and to 570 ± 44 nmol/liter by UTP. Extracellular Ca^{2+} depletion did not prevent $[Ca^{2+}]_i$ rise. The nucleotides ATP, [β,γ-imido]-ATP, and UTP also stimulated IP_1 formation by 4869 ± 200 cts/well, 2588 ± 199 cts/well, 2707 ± 49 cts/well, respectively. The P_{2X} receptor agonist [α,β-CH_2]-ATP did neither stimulate a $[Ca^{2+}]_i$ rise nor desensitize subsequent ATP response. The P_{2Y} receptor agonist 2-methylthio-ATP (10^{-3} M) stimulated $[Ca^{2+}]_i$ rise to peak at 532 ± 43 nmol/liter. Adenosine, a P_1 receptor agonist, AMP and CTP had no effect on $[Ca^{2+}]_i$ and IP_3 level. ATP and UTP effects were similar. Maximal effect of either nucleotide could not be increased by exposure of gEC to ATP and UTP (554 ± 38 nmol/liter). In summary: In gEC, ATP analogues and UTP may activate PLC leading to IP_3 generation and rise in $[Ca^{2+}]_i$. These effects are mediated by a common nucleotide receptor or distinct purine and pyrimidine receptors. Since $[Ca^{2+}]_i$ is known to be involved in prostacycline and EDRF production, these nucleotides therefore may antagonize the contractile response in gMC and thus, gEC may contribute to the local regulation of glomerular capillary flow and GFR.

A method for detecting proteinuric factors in patient sera. *J.U. Steiger, M. Hermle, F.P. Brunner, G. Thiel, and H.A. Bock, Abteilung Nephrologie, Kantonsspital Basel, Switzerland.* Sera of nephrotic patients have been reported to contain a factor which increases albumin permeability and whose presence is associated with recurrent proteinuria in kidney grafts. We have established an *in vitro* detection system for such factors which is based on the measurement of albumin permeability in single rabbit glomeruli. Glomeruli without Bowman's capsule are obtained by fractional sieving and held with a micropipette during sequential exchanges of superfusion chamber fluid. Glomerular volume is measured with an image analysis system. After equilibration in 5% albumin (oncotic pressure = 19.6 mm Hg), the chamber fluid is replaced by first iso-oncotic and then hypo-oncotic dextran (molecular wt 250,000). A normal, albumin-impermeable glomerulus will keep its size when changed to iso-oncotic dextran and will increase with hypo-oncotic dextran due to "reverse filtration." In contrast, a permeable glomerulus will shrink in iso-oncotic dextran, since the inward oncotic force (albumin) is inferior to the outward force (dextran), resulting in glomerular water loss. The oncotic pressure of a dextran solution which creates the same volume as the 5% albumin concentration is obtained by interpolation (π_0) and albumin permeability Φ is calculated as $1 - \pi_0/\pi_{Albumin}$. Normal rabbit glomeruli were impermeable to albumin (Φ = 0.04 ± 0.04, N = 10, mean ± SEM), even when preincubated with sera of 3 healthy individuals (0.06 ± 0.02, N = 9). Preincubation with protamin (100 U/ml), which neutralizes anionic charges of the glomerular basement membrane significantly increased permeability to 0.58 ± 0.07 (N = 13, $P < 0.001$). Similar increases in permeability were found when rabbit glomeruli were incubated with serum of a patient with membranous glomerulonephritis (recurrent in two consecutive transplants; Φ = 0.49 ± 0.07, N = 7) and with serum of a patient with recent onset nephrotic syndrome (Φ = 0.60 ± 0.05, N = 5). In conclusion, the present system is capable of detecting proteinuric factors in patient sera. It could serve as a detector system for identifying the nature of these factors. In addition, it might be useful for identifying patients which are at risk for recurrent transplant glomerulonephritis.

Mesangial matrix metalloproteinases and their role in glomerulonephritis. *H.P. Marti and D.H. Lovett, Department of Medicine, San Francisco VAMC-University of California at San Francisco, San Francisco, USA.* The integrity of the glomerular extracellular matrix (ECM), which includes the glomerular basement membrane and the mesangial matrix, is a prerequisite for normal glomerular structure and function. The key components of the glomerular ECM are type IV and V collagens, sulphated proteoglycans, laminin, entactin and fibronectin. Mesangial cells play an important role in both the synthesis and degradation of the matrix. ECM proteins are degraded by a group of extracellularly active proteinases, the matrix metalloproteinases (MMP). These enzymes belong to the collagenase supergene family, which are secreted in latent forms and depend on zinc and neutral pH for maximal activity. Due to the complex composition of the ECM, we have postulated that several matrix-degrading metalloproteinases must exist, especially within the centrally located glomerular mesangium. A polymerase chain reaction (PCR)-based homology cloning strategy was developed to characterize the spectrum of MMP expressed by cultured human and rat mesangial cells. Exploiting this method, we defined at the molecular level the structure of human forms of punctuated metalloproteinase (PUMP-1) and interstitial collagenase, along with a rat 72-kDa type IV collagenase. After incubation with the inflammatory cytokines interleukin 1 and tumor necrosis factor, a significant increase in the amount of mRNAs of PUMP-1 and 72-kDa type IV collagenase in mesangial cells was observed. Increased PUMP-1 synthesis *in vivo* was demonstrated within clinical biopsy specimens of pauci-immune rapidly progressive glomerulonephritis, in which mesangial hypercellularity was a noticeable feature. After induction of acute anti-Thy 1.1 nephritis, a model of immune complex-mediated glomerulonephritis in rats, augmented synthesis of mesangial 72-kDa type IV collagenase was documented. The probably cytokine-mediated enhanced expression of mesangial MMP may contribute to the evolution of glomerular destruction in mesangial cell-mediated forms of glomerulonephritis. Therefore, selective modification of activity and expression of mesangial MMP may lead to new kinds of therapy for glomerular inflammatory disease.

LPS modifies the plasminogen activator/plasmin system of the murine kidney. *S. Moll, J.A. Schifferli, J. Huarte, J.D. Vassalli, and A.P. Sappino, Laboratoire d'Immunonéphrologie, Département de Morphologie et Division d'Oncologie, Centre Médical Universitaire, Genève, Switzerland.* Recent observations have shown that urokinase-type

(u-PA) and tissue-type (t-PA) are produced by distinct epithelial cells in the murine kidney and released into the urine, suggesting a role for these enzymes in the maintenance of tubular patency. In order to determine whether septic shock might modify the renal production of PAs, we treated adult mice with LPS and analyzed the expression of u-PA, t-PA and PAI-1 mRNAs in the kidney by the combined use of Northern blots and in situ hybridizations. The enzymatic activity of u-PA and t-PA was assessed by histological zymography on tissue sections and by SDS-PAGE zymography of urine. We observed that a single i.p. injection of 100 μg induced a dramatic reduction in u-PA mRNA levels in proximal and distal tubules. This decrease in mRNA corresponded to a reduction in u-PA activity in the kidney and in urine. By contrast, t-PA mRNA levels increased in glomerular cells and in papillary collecting ducts. This increased content of t-PA mRNA correlated with an increased expression of activity *in situ* and in pelvic urine. Finally, there was a concomitant increase in PAI-1 mRNA, which was present throughout the kidney. In addition, PA-PAI complexes were detected in the urine of LPS treated animals but not in controls. These results indicate that a single LPS injection alters the plasmin-catalyzed proteolytic balance in the murine kidney and suggest that a transient decrease in tubular proteolysis may account for some of the functional alterations accompanying septic shock.

Assessment of GFR from the k × body height/P creatinine formula. *A. Bueva and J.-P. Guignard, Service de Pédiatrie, CHUV, Lausanne, Switzerland.* GFR per body surface area being proportional to body height and inversely proportional to the plasma creatinine (P_{Cr}), a formula has been proposed to estimate GFR without urine collection: GFR = k × body height/P_{Cr}. The constant k is usually calculated by using creatinine clearance (C_{Cr}) as an estimate of GFR. In order to evaluate the possible variability of k according to the patient's state of diuresis, a retrospective analysis of 1768 clearance studies in children aged 1 to 16 years has been made, and the value of k calculated from both inulin clearance (C_{in}) and C_{Cr}. Body height and P_{Cr} were expressed in cm and mg/dl, respectively. The results showed that: (a) C_{Cr} correlates significantly with urine flow rate ($y = 87.15 + 6.13x$; $r = 0.820$; $P < 0.001$); (b) k values calculated from C_{Cr} consequently increase linearly with urine flow rate ($\dot{V}$), values varying from 0.60 at $\dot{V}$ below 5 ml/min × 1.73 m^2 to 0.84 at $\dot{V}$ above 15 ml/min × 1.73 m^2; and (c) the correlation between C_{in} and k × body height/P_{Cr}, where k had been calculated from C_{Cr}, showed a substantial scatter of values. A prospective study in 44 additional children studied in hydropenic conditions and after water loading confirmed the finding of elevated values of k during water diuresis (0.72 ± 0.30 SD) as opposed to hydropenia (0.56 ± 0.10 SD). We conclude that to be useful, the k value must be calculated from C_{in} and the clearance studies performed in strictly standardized conditions.

Karyomegalic interstitial nephritis: An HLA-associated disease? *M. Spoendlin, F. Brunner, G. Thiel, and M. Mihatsch, Departments of Internal Medicine and Pathology, University of Basel, Basel, Switzerland.* Systemic karyomegaly associated with chronic interstitial nephritis was first described in 1978 by Mihatsch reporting on three cases. Two of them were brothers. Only two other cases with similar renal biopsy findings are known from the literature. We now report a further case together with an investigation of his family. Case report: A 35 year old athletic physical training instructor was referred because of decreased renal function. From age 22 to 28 he had been suffering from recurrent episodes of fever, arthralgia and myalgia of undetermined origin. Thereafter he had frequent upper respiratory infections and abscesses of the skin. Slowly deteriorating renal function and mild proteinuria were first noted at age 26. At referral, there were no abnormal physical findings, blood pressure 135/65 mm Hg, plasma creatinine 221 μmol/liter, 24-hour creatinine clearance 50 ml/min and proteinuria 920 mg/24 hours. Urinalysis was unremarkable except for proteinuria and mild glucosuria. A renal biopsy disclosed interstitial fibrosis and many tubular cells with large polymorphic nuclei (as described in the previous cases). The same karyomegalic cells were also found in urinary cytology. Screening for heavy metal poisoning, viral infection and immunodeficiency was negative. Family investigation: Renal function and urinary cytology of the parents, the sister and one of the sons were normal. The urine of the other 12 years old son showed karyomegalic cells. His renal function was normal but he had a history of recurrent infections with chronic otitis media. Our findings support the association of karyomegaly and interstitial nephritis as an entity. A genetic predisposition, perhaps linked to the HLA-antigens A9 and B35, seems likely. All three previous cases as well as the present case and his karyomegalic son tested positive for HLA A9 and B35. The common clinical features of the four patients whose renal biopsy was examined in Basel were male sex, frequent infections, glucosuria and onset of renal failure during the third decade.

Three years experience with a percutaneously inserted double lumen catheter for permanent hemodialysis access: A prospective study. *P. Ruedin, C. Laverrière, A. Pechère Bertschi, C. Stoermann Chopard, T. Etienne, M.C. Marti, and M. Leski, Division de Néphrologie et Département de Chirurgie, Hôpital Cantonal Universitaire, Genève, Switzerland.* Over a three year period, 63 "Perm-cath" catheters (PC), were inserted percutaneously under local anesthesia into 56 patients (mean age: 66.5 ± 1.7 years SEM) undergoing maintenance hemodialysis. PC are cuffed dual lumen catheters made of soft silicone rubber. Sixty PC were placed via the right internal jugular vein and three via the left internal jugular vein; the catheter tip was positioned into the right atrium. The procedure was performed with full surgical asepsis and under vancomycin prophylaxis. PC was placed as first choice vascular access in 32 patients, most of them suffering from cardiac insufficiency, ischemic heart disease or peripheral vascular disease. There were five minor exit-site bleedings and two local hematomas, treated conservatively, following PC insertion. Duration of the PC use ranged from 0.5 to 24.5 months (total duration: 422.5 months). The actuarial PC survival rate at 1, 3, 6, 12 and 24 months was 98, 92, 87, 83 and 83%, respectively. Obvious and suspect exit-site infection rates were 0.54 and 1.34 per year of catheter use, respectively. There was no episode of septicemia. Coumadin was given in 28 patients and aspirin or dipyridamol in seven patients; in 28 cases, patients were free of anticoagulant treatment. Problems related to inadequate blood flow through the PC occurred 10.54 times per year of PC use. These episodes were treated with urokinase (25,000 IU) given into catheter lumen. No clinical evidence of vein thrombosis was encountered during the study. Seven PC were removed (spontaneously in 2 cases) because of exit-site infection (4) or intractable blood flow difficulties (3). This prospective study shows that percutaneous insertion of the PC is safe. PC provides a reliable and long-lasting access for hemodialysis, especially when means of peripheral access are exhausted or if arteriovenous shunt is contraindicated. The rate of infectious complications is very low and no case of life-threatening infection occurred. Blood flow difficulties remain the principal problem in our experience.

Risk and benefit of oral calcitriol therapy in chronic hemodialysis patients. *D. Kiss, K. Donauer, and K. Gyr, Dialysestation, Medizinische Klinik, Kantonsspital Liestal, Switzerland.* To investigate the risk and benefit of oral calcitriol therapy, we analyzed in 30 chronic hemodialysis (HD) patients the evolution of the biochemical bone markers (serum calcium, phosphorus, alkaline phosphatase, i-PTH) retrospectively. To keep serum phosphorus below 1.8 mmol/liter, the patients were treated either with aluminium hydroxide (group I, $N = 12$) or with calcium carbonate (group II, $N = 18$), and the treatment was strictly adjusted every month. By this schedule the mean (± SD) concentration of i-PTH fell significantly lower in group II (126 ± 48 ng/ml vs. 221 ± 57 ng/ml). Serum phosphorus concentration was comparable in both groups (group I 1.78 ± 0.38 mmol/liter and in group II (1.73 ± 0.33 mmol/liter). In case of insufficient suppression of PTH activity (i-PTH > 200 ng/ml) the patients were treated with oral calcitriol (0.25 to 0.5 μg/day) additionally ($N = 8$ in group I/$N = 6$ in group II). In case of increased serum calcium (>2.6 mmol/liter) the calcium concentration of the dialysate was lowered. Five of the eight patients of group I and four patients of group II developed hypercalcemia (serum calcium > 2.8 mmol/liter). In contrast to aluminium hydroxide calcium containing phosphate binders have a stronger effect on the suppression of PTH secretion. Oral calcitriol therapy lowers PTH activity additionally, therefore only in patients with high PTH activity calcitriol therapy might be used. The lowering of the calcium concentration of the dialysate may lead to an increase of PTH activity again, and does not always prevent hypercalcemia. Hyperphosphatemia and hyperparathyroidism should be treated with calcium containing phosphate binders only. Oral calcitriol therapy should only

be used in patients with insufficiently suppressed PTH activity, and this must be done under strict control of the biochemical bone markers.

Calcium acetate or aluminium hydroxide to treat hyperphosphatemia in maintenance hemodialysis? A prospective randomized cross-over study. *F. Rohner, H.R. Räz, and P. Sandoz, Bürgerspital, Solothurn, Switzerland.* Calcium acetate (CaAc) was compared with aluminium hydroxyde (AlOH) as a phosphate binder in a prospective, randomized cross-over study including 33 patients on maintainance hemodialysis. Changes in serum levels of phosphorus, calcium and acid-base homeostasis were evaluated. The data of seven patients were excluded from analysis for various reasons. While taking AlOH, six of 26 patients reported gastrointestinal side effects, compared to only one of 26 taking CaAc. CaAc resulted in a slightly better control of mean serum phosphate levels (1.75 mmol/liter vs. 1.91 mmol/liter, P = NS) when ingested in the same daily dose. Mean calcium levels rose from 2.37 to 2.49 mmol/liter ($P < 0.01$) in patients taking CaAc. Six of 26 patients developed asymptomatic hypercalcemia (Ca > 2.7 mmol/liter) while taking CaAc. This was easily controlled by omission of calcitriol and/or reduction of calcium levels in dialysis fluids from 1.75 mmol/liter to 1.25 mmol/liter in all but one patient. CaAc did not clearly improve uremic acidosis. Serum potassium levels remained unchanged. Therefore, CaAc is a well tolerated and effective alternative to AlOH in the control of hyperphosphatemia. Because of frequent hypercalcemia regular serum calcium controls are mandatory.

L-carnitine improves vascular refilling in hemodialysis patients during ultrafiltration. *J. Záruba, W. Probst, A. Knoflach, and U. Binswanger, Nephrologische Station, Departement Innere Medizin, Universitätsspital Zürich, Zürich, Switzerland.* The reports on carnitine supplementation and its benefits in patients undergoing chronic hemodialysis are controversial. However, recently carnitine was found to reduce the rate of intra-dialytic hypotensive episodes and muscle cramps. To study the mechanism involved in this observation, we measured vascular refilling prior to carnitine supplementation and after four weeks of carnitine administration (1 g i.v. after each dialysis session) in four hemodialysis patients. The rate constant of vascular refilling (Lp = ml × min^{-1} × mm Hg^{-1} × 50 kg^{-1}) was determined from the changes of blood volume and of colloid-osmotic pressure and normalized for 50 kg lean body mass. The relative changes of blood volume were monitored continuously by means of ultrasound velocity, and the changes of colloid-osmotic pressure were calculated from plasma protein concentrations. At the beginning of the dialysis session the patients were subjected to an "ultrafiltration pulse" for 20 minutes. The volume ultrafiltrated during this "pulse" was equivalent to the necessary ultrafiltration-volume per hour to reach the patients ideal predialysis weight. After four weeks of carnitine supplementation the serum levels of free carnitine increased from 36.8 ± 9.7 to 127.5 ± 32.9 (Mean ± SD, paired t-test, $P < 0.02$). Lp increased from 3.81 ± 0.58 to 7.95 ± 2.82 (Mean ± SD, $P < 0.02$, paired t-test). This corresponds to a mean increase by more than 100%. By improving the vascular refilling rate carnitine might contribute to better ultrafiltration tolerance during hemodialysis.

Adequacy of dialysis in high risk patients with end-stage renal disease on continuous peritoneal dialysis (CAPD). *A. Edward and J.A. Cerutti, Ospedale Civico, Lugano, Switzerland.* Adequacy of dialysis has become a crucial factor in patient evaluation in all long-term dialysis programs. The purpose of this study is to explore the usefulness of urea kinetic modeling (UKM) and total weekly creatinine clearance (C_{Cr}) in relation to the clinical outcome and mortality in a high-risk CAPD population on conventional therapy (a fixed daily dose of dialysis with standard solution). The population consisted of 13 females and 17 males with a mean age of 64 ± 12.42 years with a minimum of 38 and a maximum of 83 years, a mean time of dialysis of 30 ± 26.6 months with a minimum of 0.5 and a maximum of 95 months. To define the clinical outcome, we employed the scoring system of the University of Missouri and found 70% of the population in the good and intermediate groups with 30% falling under the poor grouping. The characteristics of the three groups are:

Population	Total	Good	Intermediate	Poor
Male	17	7	6	4
Female	13	5	5	3
Attributes				
Total C_{Cr} *liters/week*	62.4 ± 27.8	82.1 ± 25.9	55.0 ± 12.4	36.5 ± 19.4
Residual C_{Cr} *liters/week*	21.9 ± 4.59	40.6 ± 25.3	9.79 ± 14.8	4.45 ± 6.11
PCR *g/kg standard weight*	0.94 ± 0.23	0.99 ± 0.19	0.94 ± 0.26	0.86 ± 0.23
Albumin *g/liter*	37 ± 0.4	38 ± 3.3	37 ± 3.1	34 ± 6.7
Total weekly Kt/V_{urea}	2.18 ± 0.83	2.64 ± 0.85	2.14 ± 0.52	1.58 ± 0.48
Urinary weekly Kt/V_{urea}	0.56 ± 0.70	1.00 ± 0.77	0.28 ± 0.44	0.12 ± 0.17

We arrived at the following conclusions: (1) There is not a strong correlation between Kt/V_{urea}, PCR, or total weekly creatinine clearance and the clinical assessment. (2) Kt/V_{urea} and total weekly creatinine clearance can be considered a good index for defining the lower limit below which morbidity and mortality increase. (3) High risk patients have the same prognosis as normal CAPD patients, provided the recommended criteria for adequacy are observed: $Kt/V_{urea} > 1.5$, total creatinine clearance > 50 liters per week, and a PCR > 0.8 g/kg standard weight/day. (4) When the recommended criteria for adequate dialysis are no longer obtainable, an adjustment of the therapy prescription must be made.

Adsorption of complement factor D by polyacrylonitrile dialysis membranes. *M. Pascual, O. Plastre, P. Ruedin, and J.A. Schifferli, Laboratoire d'Immunonéphrologie, Division de Néphrologie, Hôpital Cantonal de Genève, Genève, Switzerland.* Polyacrylonitrile (PAN) membrane activates complement poorly, and has been shown to adsorb C3a, the main anaphylatoxin released during complement activation. Other studies have indicated that incubation of serum with PAN was responsible for a loss of complement activity which could not be related to activation. In the present work we investigated whether factor D, an essential enzyme of the alternative pathway of complement, might be adsorbed on PAN. *In vitro*, there was a loss of hemolytic factor D when NHS was incubated with PAN dialysis fibers, whereas no loss was observed with cuprophan (Cu) fibers. In addition, there was a dose and time dependent binding of purified radiolabeled factor D to PAN, but not to Cu. Factor D released from PAN by 2 M NaCl restored AP function in serum immunochemically depleted of factor D (RD). By contrast, factor D was not functional while adsorbed to PAN fibers. The eluate from a PAN dialysis filter which had been used for dialysis in a patient with ESRF contained 38.4 mg of hemolytic factor D, representing 34% of the proteins eluted, thus indicating that factor D adsorption was very selective. By immunoblotting, antigenic factor D from the PAN eluate was shown to be identical to purified human factor D. In six chronic hemodialysis patients, there was a 81.4% decrease in their plasma hemolytic factor D after dialysis with PAN. No factor D was found in the dialysis fluid suggesting that PAN membrane removed factor D mainly by adsorption. By calculation it was estimated that dialysis on PAN removed 48 mg of factor D per dialysis session. In five patients dialyzed with cellulose acetate, there was a 9.6% significant decrease in hemolytic factor D that could be explained by mass transfer of the protein to the dialysis fluid. In conclusion, PAN has a selective capacity to adsorb and remove factor D, a reaction that might contribute to the diminished capacity of PAN membrane to activate complement during hemodialysis.

Impact of dialysis modality on body composition (BC) in patients with end-stage renal disease (ESRD) as assessed by dual X-ray absorptiometry (DXA). *H. Saxenhofer, F.F. Horber, J.-P. Casez, and Ph. Jaeger, Medizinische Universitätspoliklinik, Inselspital, Bern, Switzerland.* Whole body DXA accurately assesses BC in different compartments such as arms, trunk, legs, and uncovers subtle changes of lean body mass (LBM), fat mass (FM) and bone mineral content (BMC). Whether hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) alters BC differently is unknown. Therefore, using DXA we investigated 47 HD and 30 CAPD patients as well as 64 healthy controls (C) matched for age, sex, and body mass index. Compared to C, cortical (448 ± 16 g vs. 524 ± 21; $P < 0.01$) and trabecular (1151 ± 41 g vs. 1285 ± 34; $P < 0.02$) bone compartments were lower in ESRD patients irrespective of the dialysis modality applied. Total FM was similar between the three groups investigated. However, the ratio of upper to lower FM was higher in female CAPD (1.28 ± 0.10 vs. 0.96 ± 0.08, $P < 0.05$) and HD patients (1.10 ± 0.10 vs. 0.83 ± 0.07, $P < 0.05$), whereas male dialysis patients demonstrated similar FM distribution to C. LBM of the trunk and arms were similar in HD and CAPD patients as compared to C; however, LBM of the legs was lower in male (14.9 ± 0.3 kg vs. 17.1 ± 0.4; $P < 0.001$) and female (10.2 ± 0.3 kg vs. 11.6 ± 0.2; $P < 0.001$) HD and CAPD patients. Our data suggest that: (1) both, cortical and trabecular bone are significantly affected in ESRD independent of the dialysis modality used; (2) female but not male patients have increased central fat stores in the presence of normal total FM; and (3) both, HD and CAPD are associated with significant muscle wasting.

Altered body composition in stable renal transplant patients on cyclosporine monotherapy: Impact on lipid and carbohydrate metabolism. *F.F. Horber, R.L. Mathieu, A. Montandon, and Ph. Jaeger, Medizinische Universitätspoliklinik, Inselspital, Berne, Switzerland.* Altered body fat distribution and muscle wasting are classically encountered in renal transplant patients (RTP), probably as a consequence of immunosuppressive therapy with glucocorticoids. Several months to years after transplantation, a subgroup of patients can be maintained on a immunosuppressive monotherapy with cyclosporin A (CsA). Whether this therapeutic modality is associated with normalization of altered body fat distribution and muscle mass remains to be determined. Therefore, 18 RTP, (9 males and 9 females, 64 ± 5 months since transplantation; CsA-monotherapy: 38 ± 7 months) and 18 age, sex and body mass index matched healthy volunteers (N) were investigated using indirect calorimetry (Deltatrac) and dual energy X-ray absorptiometry (Hologic QDR 1000 W). Lean body mass (LBM) was decreased in patients, mostly due to loss of striated muscle in the legs (14.0 ± 0.7 vs. 16.5 ± 1.0 kg, $P < 0.01$, RTP vs. N). In RTP fat mass was increased in the head (1.13 ± 0.04 vs. 1.01 ± 0.03, $P < 0.01$) and trunk (12.6 ± 1.2 vs. 10.2 ± 1.0, $P < 0.01$), but was similar in the extremities as compared with N. Interestingly, resting energy expenditure (REE) was increased in RTP by more than 10% as compared with N (32.5 ± 1.0 vs. 29.5 ± 0.6 kcal/kg LBM, $P < 0.05$). Plasma insulin and glucose concentrations as well as total serum cholesterol (C) and triglyceride levels and the ratio of LDL-C to HDL-C all were elevated ($P < 0.01$) in RTP as compared with N. In conclusion, RTP on an immunosuppressive monotherapy with CsA display decreased muscle mass despite discontinuation of prednisone therapy. The increased upper body fat might, at least in part, account for peripheral hyperinsulinemia and dyslipidemia observed in RTP even years after successful kidney transplantation. CsA-induced futile substrate cycling might explain increased REE in RTP.

Changes in body composition and fuel metabolism early after kidney transplantation are sex specific and mediated by glucocorticoids. *U. Steiger, J.P. Casez, Ph. Jaeger, A. Montandon, C. Descoeudres, and F.F. Horber, Policlinic of Medicine, University Hospital, Berne, Switzerland.* Kidney transplant patients (KTP) exhibit decreased muscle mass and increased fat mass. Whether this altered body composition is due to glucocorticoid therapy or to preexisting renal failure is unclear. Therefore, 13 KTP and 13 age, sex and body mass index matched normal healthy volunteers (N) were studied by whole body densitometry (Hologic QDR 1000 W) and indirect calorimetry (Deltatrac). N were studied only once, while KTP were seen first 45 ± 2 (mean ± SEM) days after kidney transplantation (KT) [daily dose of prednisone (DDP): 0.29 ± 0.03 mg/kg body wt/day] and again after 152 ± 8 (DDP: 0.24 ± 0.03 mg/kg/day) and 492 ± 6 days (DDP: 0.17 ± 0.02 kg/day). All KTP were advised to restrict their caloric intake to resting energy expenditure (REE) plus 20% with a protein content of 1.2 g/kg body wt. In KTP at 42 days after KT, lean mass of the legs was lower by 12.7 ± 3.3% ($P < 0.01$) than in N, whereas no difference in fat mass and REE could be detected between KTP and N. In contrast, lipid oxidation (LOX) was lower ($P < 0.01$), whereas carbohydrate oxidation (COX) was higher ($P < 0.01$) than in N. After 150 and 492 days, fat mass increased by 3.9 ± 0.5 and 4.9 ± 0.5 kg respectively in males, but not in females (0.1 ± 0.5 kg). Segmental analysis of the fat compartments revealed an increased fat mass in all compartments (head, trunk, legs, arms) in males, whereas in females an increment in fat mass was detected only in the head ($P < 0.01$). After 492 days lean mass of arms and legs increased by 1.4 ± 0.4 kg ($P < 0.05$), independent of sex. LOX increased, whereas COX decreased with decreasing DDP ($P < 0.01$), being similar between KTP and N after 492 days of observation. In conclusion, compared with N, KTP exhibit decreased leg muscle mass which increases slightly during 18 months after KT. KTP exhibit a lipogenic potential (decreased LOX) due to immunosuppressive therapy with glucocorticoids. Moon face is the only characteristic feature of fat mass changes induced by exogeneous therapy with prednisone in KTP. Reducing DDP to less than 0.1 mg/kg body wt/day allows KTP to normalize fuel metabolism.

Serum hippuric acid concentration in renal allograft rejection and ureteric obstruction. *Andreas Knoflach and Ulrich Binswanger, Nephrologische Abteilung, Departement für Innere Medizin, Universitätsspital, Zürich, Switzerland.* Plasma from 35 renal allograft recipients (21 males and 14 females) was sampled daily and analyzed for hippuric acid (HA) by HPLC reversed-phase-technique and serum creatinine. Twelve of these patients showed an acute renal allograft rejection or a ureter obstruction as proven by clinical signs and biopsy as well as radiography or ultrasound, respectively. We found a mean increase of serum hippuric acid in patients with acute rejection by 39.9 μmol/liter from baseline (range 20.4 to 115.5) three days after initial increase; this rise was observed already 24 hours before the mean serum creatinine increased by 107.1 μmol/liter (range 21 to 193). In case of ureter obstruction HA rose by 1.6 μmol/liter (range 1 to 8.2), significantly less than elevations due to rejection. The increase in creatinine however amounted to 65.3 μmol/liter (range 22 to 140) and was not different as compared to the change in rejecting patients. Successful antirejection treatment coincided with a decrease of serum HA starting 24 hours earlier than the decrease of the serum creatinine concentration.

	Acute allograft rejection			Ureteric obstruction	
	Creatinine μmol/liter	Hippuric acid μmol/liter		Creatinine μmol/liter	Hippuric acid μmol/liter
Pat. 1	110–131	n.d–43.0	Pat. 7	80–124	n.d–n.d
Pat. 2	108–267	n.d–26.3	Pat. 8	137–176	n.d–9.2
Pat. 3	79–120	n.d–11.2	Pat. 9	126–186	n.d–n.d
Pat. 4	324–517	3.8–30.7	Pat. 10	152–237	n.d–n.d
Pat. 5	1023–1069	156.5–272	Pat. 11	99–121	n.d–n.d
Pat. 6	153–336	9.4–29.9	Pat. 12	129–269	5.8–5.8

First measurement: baseline value; second measurement: 3 days after initial rise. n.d: <3 μmol/liter (detection limit)

Our data suggest that serum hippuric acid, which is excreted by tubular secretion, could be a sensitive and early marker of acute allograft rejection. Furthermore, it seems to discriminate between acute renal allograft rejection and ureteric obstruction.

Azathioprine hypersensitivity mimicking relapses of Goodpasture's syndrome. *M. Stetter, M. Schmidli, and R. Krapf, Medizinische Klinik B, Kantonsspital, St. Gallen, Switzerland.* Side effects due to azathioprine (the nitroimidazole derivative of 6-mercaptopurine) can be classified as toxic (myelosuppression, hepatotoxicity) and idiosyncratic (that is, fever, rigors, arthralgias, pneumonitis and gastrointestinal symptoms). While the toxic effects are due to 6-mercaptopurine, the hypersensitivity reactions are believed to be caused by the nitroimidazole moiety. A 21 year old male patient developed terminal renal failure

due to Goodpasture's syndrome (rapidly progressive glomerulonephritis with linear IgG-deposits, positive circulating anti-basement membrane antibodies, AGBM). He was treated with CAPD and later hemodialysis and received two renal grafts at age 23 and 27, respectively. He received a total of four courses of azathioprine treatment: 1× for Goodpasture's syndrome, and 3× for rejection episodes. Each course was followed within four to seven days by high fever, rigors, arthralgias, diarrhea, myalgias and pulmonary infiltrates with hemoptoe, which were considered to be consistent clinically with relapses of Goodpasture's syndrome. However, all signs and symptoms resolved completely within days upon discontinuation of azathioprine. AGBM were never elevated and—during one episode—relapse of Goodpasture's could be excluded by open lung biopsy. Treatment of a subsequent rejection episode with 6-mercaptopurine was tolerated without side effects. We conclude that azathioprine hypersensitivity can mimick relapse of Goodpasture's syndrome. The hypersensitivity was probably caused by the nitroimidazole moiety of azathioprine. Thus, differential diagnosis of Goodpasture's syndrome (and probably of any "pulmorenal syndrome") should include azathioprine hypersensitivity.

How living related kidney donors think about their organ donation 1 to 21 years later. *P. Sparta and G. Thiel, Kantonsspital, Universität Basel, Basel, Switzerland.* Fifty-six related kidney donors (35 females, 21 males, 17 sisters, 11 brothers, 16 mothers, 11 fathers and one grandmother) received a questionnaire with 20 questions written in their own language (eleven languages), from one up to 21.6 years after donation. Fifty-one donors completed the questionnaire. Results: (1) Fifty (98%) were still happy with their former decision to donate a kidney. (2) Eight (16%) felt they were not informed well enough before donation. (3) Ten (20%) felt that there was some non-outspoken, slight pressure within the family in favor of their donation. (4) Twelve (24%) experienced that the operation itself was worse than expected. (5) Forty-one (80%) were happy with the hospital care, 2 (4%) were unhappy, and the remaining were in between. (6). Fifteen (29%) felt esthetically slightly disturbed by the surgical scar. (7) Thirty-nine (76%) have no or not more back pain than before donation. (8) Fourteen (27%) had some concrete propositions as to what could be done better by the involved physicians and surgeons (7: more attention post-operatively). (9) Thirteen (25%) remained unpaid for a variable postoperative period, as long as they were unable to work. (10) The duration of income losses varied from nine to 61 days (mainly one month). (11) The following physical complications occurred related to donation: vein thrombosis on the leg (3), pulmonary embolism and cardiac arrhythmia (one obese mother), pain/itching/sensitivity losses around the surgical scar (6), more tired (3 patients, aged 54, 63 and 66 years). (12) Fourteen drugs are currently consumed that were not taken before donation and could be potentially related to donation (antihypertensive agents 2; diuretics: 1, NSAID and other analgesics: 10; antidepressants: 1). (13) Other severe diseases since donation: stomach cancer in one. (14) Blood pressure was normal before donation in 48 (94%) and increased in the remaining three. (15) Blood pressure is believed to be normal still in 31 (74%), "too low" in six (12%) and increased in another seven (14%). (16) The family doctor found some proteinuria after donation in one and no proteinuria in 26. The remaining 24 did not know anything about their urine. (17) The current state of health was felt to be good or fair in 47 (92%). (18) The personal relation between donor and recipient has improved since donation in 14 (27%) or remained unchanged in 35 (69%), but got worse in one. (19) Two donors felt the recipient should express more gratitude. (20) The question whether the behavior of close family members in regard to donation has disappointed the donor was only answered positively by one. Conclusions: Almost all living related donors remain in favor of living donation (98%), but the procedure was followed by some physical, social and psychological problems, which transplant surgeons and physicians should know about, since the problems can be solved at least partly.

Evidence for two populations of Na-K-ATPase defined by their ouabain sensitivity along the rat nephron. *E. Féraille, M. Rousselot, and H. Favre, Division of Nephrology, Hôpital Cantonal Universitaire, Genève, Switzerland.* By now, three isoforms of the α subunit of the Na-K-ATPase have been identified. The α1 isoform exhibits a low affinity for the specific inhibitor ouabain, whereas the α2 and α3 isoforms have a high affinity for ouabain. In the kidney the presence of α isoforms other than α1 is still controversial. This study was designed to provide evidence for the presence in the rat nephron of different isoforms by measuring the ouabain sensitivity of the Na-K-ATPase in single well-identified specific nephron segments. Proximal convoluted tubule (PCT), medullary thick ascending limb of Henle (MTAL), and cortical collecting duct (CCD) were obtained by microdissection. The ouabain sensitivity of the Na-K-ATPase was determined by measuring the Na-K-ATPase activity in the presence of ouabain concentrations ranging from 10^{-8} M to 10^{-3} M. The inhibition curves exhibited a complex pattern and were fitted using a non-linear regression analysis. This procedure allowed us to demonstrate, in each segment, the presence of two populations of Na-K-ATPase characterized by their ouabain sensitivities. The apparent Ki of the high sensitive population were $1.4 \cdot 10^{-6}$ M, $8.8 \cdot 10^{-6}$ M, $1.1 \cdot 10^{-6}$ M, whereas the apparent Ki of the low sensitive population were $2.6 \cdot 10^{-4}$ M, $4.6 \cdot 10^{-4}$ M, $1.8 \cdot 10^{-4}$ M in PCT, MTAL and CCD, respectively. The relative proportion of these two populations differed from one segment to the other. High versus low ouabain sensitive population of Na-K-ATPase: PCT 40 versus 60%, MTAL 20 versus 80%, and CCD 45 versus 55%, respectively. In conclusion, our results strongly suggest the presence of at least two different isoforms of the Na-K-ATPase, coexisting in the same nephron segment.

Rapid stimulation of Na^+/H^+-exchange by $1,25(OH)_2$ vitamin D_3: Interaction with PTH-dependent inhibition. *Ulrich Binswanger, Corinna Helmle-Kolb, Judith Forgo, Branka Mrkic, and Heini Murer, Institut für Physiologie, Universität Zürich, Switzerland.* Opposum kidney (OK) cells were grown to confluency and pH_i was measured at the single cell level using BCECF. Apical Na^+/H^+- exchange activity was quantified as rate of Na^+- dependent pH_i-recovery from an acid load. Superfusion with $1,25(OH)_2$ Vit D_3 (10^{-8} M) for one minute led to a stimulation of Na^+/H^+-exchange (57 ± 46%, mean ± SD; $P < 0.01$, paired t-test); this effect vanished after five minutes of exposure. Superfusion with PTH (5 minutes, 10^{-8} M) led to a decrease in Na^+/H^+-exchange activity (29 ± 15%; $P < 0.01$); one minute exposure to $1,25(OH)_2$ Vit D_3 during PTH perfusion (5 minutes) led to a stimulation of Na^+/H^+-exchange (36 ± 22%; $P < 0.001$). Simultaneous addition of $1,25(OH)_2$ Vit D_3 and PTH also led to a stimulation of Na^+/H^+-exchange activity (30% and 34%; measured after two minutes; $N = 2$). PTH (but not $1,25(OH)_2$ Vit D_3) was found to increase intracellular cAMP-content (RIA) and Ca^{++}-levels (Fura-2, cell suspensions). The PTH-dependent increase in Ca^{++}-concentration was unaffected by $1,25(OH)_2$ Vit D_3. The PTH-dependent accumulation of cAMP was lowered by the addition of $1,25(OH)_2$ Vit D_3 (reduction in cAMP of about 50%). These data suggest a regulatory control (stimulation) of proximal tubular brush border Na^+/H^+-exchange by $1,25(OH)_2$ Vit D_3. This non-genomic effect might in part be explained by release from "intrinsic" or hormone-mediated cAMP-dependent inhibition of transport activity.

Potential role of IGF-I in the PTH-related deterioration of renal function induced by protein diet. *J. Caverzasio, T. Shigematsu, and J.P. Bonjour, Division de Physiopathologie Clinique, Département de Médecine, Université de Genève, Genève, Switzerland.* Recent studies from this laboratory indicate that parathyroidectomy (PTX) prevents the progression of kidney damage due to high protein diet in the subtotal nephrectomized (NX) rat model of chronic renal failure. Associated with this protection, the difference in the renal compensatory growth induced by high (HPr) compared to normal (NPr) isocaloric protein diet was completely abolished by PTX. We recently observed that in this NX model, before the development of uremia (week 16), the plasma PTH concentration was slightly but not significantly increased in sham-NXHPr (31.2 ± 3.7, $N = 8$) compared to sham-NXNPr rats (22.5 ± 1.1 pg/ml, $N = 6$) and the blood pressure was not significantly different between sham-NXHPr, sham-NXNPr and PTX-NXHPr (141.8 ± 7.4, $N = 8$, 148.3 ± 4.6, $N = 6$, 153.1 ± 3.9 mm Hg, $N = 12$, respectively). To understand the physiological mechanism responsible for this protection, the changes in either circulating or kidney content of IGF-I, a growth factor capable of influencing renal compensatory growth, was analyzed after unilateral nephrectomy (UNX). In UNX rats, the administration of a HPr diet for five days significantly increased the kidney weight (KW) (1.28 ± 0.02 g, $N = 11$) and the plasma level of IGF-I (365 ± 10 ng/ml) compared to UNX rats fed NPr

(1.15 ± 0.02 g, $N = 11$, $P < 0.001$ and 306 ± 10 ng/ml, $N = 11$, $P < 0.001$, respectively). In UNX rats fed HPr, PTX completely abolished the "compensatory" growth (1.01 ± 0.05 g, $N = 7$, $P < 0.001$) and the increased plasma level of IGF-I (246 ± 14 ng/ml, $N = 7$, $P < 0.001$). There was a highly significant correlation between the change in KW and plasma level of IGF-I in all three experimental groups ($r = 0.685$, $P < 0.001$). The kidney IGF-I content was not affected either by the protein diet or PTX. In PTX-NX rats chronically treated with physiological doses of 1,25-dihydroxyvitamin D_3 which normalized the calcemia, the "compensatory" growth and the increased plasma level of IGF-I induced by HPr were restored towards those in sham-NXHPr rats. In conclusion, the results of this study strongly suggest that circulating but not kidney content of IGF-I mediates the PTH and 1,25-dihydroxyvitamin D_3 effects on protein-induced renal compensatory growth and deterioration of kidney function in chronic renal insufficiency. Whether the circulating level of IGF-I is influenced either directly by these calciotropic hormones or indirectly by their effects on the extracellular concentration of calcium remains to be investigated.

Effects of citrate and calcium on Tamm-Horsfall glycoprotein (THP) as a modifier of calcium oxalate monohydrate (COM) crystal aggregation. *B. Hess, L. Zipperle, and Ph. Jaeger, Medizinische Universitätspoliklinik, Inselspital, Bern, Switzerland.* There has been some controversy about whether THP—the most abundant protein in urine from healthy people—inhibits or promotes the aggregation of COM crystals (COM-Aggr). We studied the effects of THP on COM-Aggr *in vitro* at pH 5.7/[NaCl] 200 mM in the presence of either 5 mM $CaCl_2$ (CA^+) or 3.5 mM citrate (CIT^+), or with both 3.5 mM citrate and 5 mM calcium (CIT^+/CA^+). THPs were individually purified from 24-hour urines of nine healthy men (N) and seven male idiopathic recurrent calcium stone formers (RCSF). COM-Aggr *in vitro* was measured in crystal slurries (0.7 mg/ml) at 37°C after adding THP to a final concentration of 40 mg/liter. All THPs were dissolved in either CIT^+ or CA^+ or CIT^+/CA^+, and intrinsic viscosities (VISC) were measured using a capillary viscometer at 25°C. All values are mean ± SEM. In CA^+, mean inhibition of COM-Aggr by all 16 THPs was −2 ± 10%; N-THPs were inhibited by 23 ± 9%, whereas RCSF-THPs did so by −34 ± 11% ($P = 0.0013$ vs. N), that is promoted COM-Aggr. VISC was higher in RCSF than in N (357 ± 52 vs. 138 ± 26 ml/g, $P = 0.0012$), indicating more polymerized THP molecules in RCSF. There was a significant negative correlation between inhibition of COM-Aggr and VISC of THPs ($r = 0.866$, slope −0.299, $P = 0.0001$), that is more polymerized THPs were weaker inhibitors of COM-Aggr. In CIT^+/CA^+ without THP (control conditions), slight promotion of COM-Aggr (−15 ± 2%, $P < 0.001$ vs. CA^+) occurred; however, all 16 THPs subsequently added were inhibitory (45 ± 5%, $P = 0.0001$ vs. CA^+), and no difference was noted between N and RCSF. VISC of RCSF-THPs was 214 ± 33 ml/g ($P = 0.034$ vs. CA^+), not different from N (186 ± 31 ml/g). In CIT^+, inhibition by all THPs increased further to 57 ± 4% ($P = 0.007$ vs. CIT^+/CA^+) without difference between N and RCSF. VISC of RCSF-THPs again decreased to 90 ± 40 ml/g ($P = 0.015$ vs. CIT^+/CA^+), indicating least polymerized THP molecules in the presence of citrate alone. In conclusion, THPs from RCSF promote COM-Aggr in CA^+, whereas N-THPs are mainly inhibitory. Since inhibition of COM-Aggr by THPs is highest and VISC lowest in CIT^+, it is suggested that citrate might play its role as an "inhibitor" of COM-Aggr, at least in part, by inducing conformational changes (depolymerization) in THP molecules, thereby turning promotory THPs into inhibitors of COM-Aggr.

Adrenalectomy (ADX) increases phospholipase A2 (PLA2) mRNA, protein, and enzyme activity. *B. Vishwanath, F.J. Frey, M.F. Dallman, and B.M. Frey, Division of Nephrology, University of Berne, Switzerland; Department of Physiology, UCSF, San Francisco, California, USA.* Clinical evidence suggests that acute withdrawal of chronic glucocorticoid therapy with suppression of endogenous cortisol production in RTX patients is associated with an increased susceptibility to rejection. Furthermore, experimental and clinical observations revealed an enhanced immunological and inflammatory response in glucocorticoid deficiency. A key enzyme of the inflammatory response is the PLA2, which releases arachidonic acid. In order to elucidate whether glucocorticoid deficiency causes PLA2 up-regulation, the expression of PLA2 mRNA and protein, as well as the enzyme activity, were quantified in rats with and without ADX. The mRNA of PLA2 was quantified by polymerase chain reaction using a constant amount of a modified PLA2 cDNA transcript as an internal standard. PLA2 message and activity varied from organ to organ with the lowest values in kidneys. The PLA2 mRNA was increased by 116 ± 24% in various tissues of ADX rats. This up-regulation of PLA2 mRNA was not due to a nonspecific effect of ADX, since the mRNA levels of other proteins (c-*fos*, c-*myc*, c-*erbβ*, methallothionein-II) remained unchanged. The increase in PLA2 mRNA in ADX rats was reflected by a corresponding increase in tissue (kidney, lung, spleen, liver) PLA2 enzyme activity and protein content as assessed by quantitative Western blot analysis. Thus, ADX increases PLA2 message, protein and activity, an observation in accordance with the increased susceptibility to inflammatory reactions in glucocorticoid deficiency.

Role of endogenous endothelin in renal hemodynamics of newborn rabbits. *D. Semama, M. Thonney, J.-B. Gouyon, and J.-P. Guignard, Service de Pédiatrie, CHUV, Lausanne, Switzerland.* Endothelin is a potent vasoconstrictor peptide produced by vascular endothelial cells, which could play a role in the physiologic regulation of the renal microcirculation. To test this hypothesis, experiments were performed in 23 anesthetized and mechanically-ventilated newborn rabbits. Renal blood flow (RBF) and glomerular filtration rate (GFR) were determined by the clearance of para-aminohippuric acid and inulin, respectively. Each animal acted as its own control. In eight newborn rabbits (group 1), a bolus injection of 5 nmol · kg^{-1} of endothelin caused a marked increase in mean blood pressure (MBP) and renal vascular resistance (RVR), leading to a significant fall in GFR (−12 ± 4%) and RBF (−16 ± 3%). A second group of animals ($N = 8$) was used for testing the *in vivo* neutralizing activity of an endothelin-1 antiserum. The antiserum was thereafter infused in seven additional newborn rabbits (group 3), in order to define the role of endogeneous endothelin in modulating the function of the immature kidney. The antiserum induced a surprising increase in RVR (+24 ± 9%, $P < 0.05$) associated with a fall in GFR (−17 ± 6%, $P < 0.05$) and RBF (−18 ± 5%, $P < 0.05$), while filtration fraction and MBP remained unchanged. The occurrence of a vasoconstrictive response to both high-dose endothelin and to its antiserum could be explained by the recent demonstration that high levels of endothelin lead to renal vasoconstriction, while lower levels induce renal vasodilatation. The present results suggest that endogenous endothelin is active at low levels in normal conditions and that this peptide plays a role in the physiologic control of renal function but not MBP.

Effects of endothelin-1 administration on renal function in newborn rabbits. *D. Semama, M. Thonney, J.-B. Gouyon, and J.-P. Guignard, Service de Pédiatrie, CHUV, Lausanne, Switzerland.* Endothelin is a potent vasoconstrictor. The renal effects of endothelin-1 were investigated in 16 anesthetized and mechanically-ventilated newborn rabbits. Renal blood flow (RBF) and glomerular filtration rate (GFR) were determined by the clearance of para-aminohippuric acid and inulin, respectively. Each animal acted as its own control. In eight newborn rabbits, a bolus injection of 5 nmol · kg^{-1} caused an initial fall in mean blood pressure (MBP) followed by a gradual but significant increase in MBP that lasted for 45 minutes. The dramatic increase in renal vascular resistance (+28 ± 4%), induced by endothelin, led to a fall in GFR (−12 ± 4%) and RBF (−16 ± 3%). In spite of the reduction of GFR and RBF, urine flow and sodium excretion rates increased significantly (+20 ± 5% and +49 ± 9%, respectively). The diuretic effect could be ascribed to an inhibition of AVP-stimulated osmotic water permeability in inner medullary collecting ducts by endothelin. The natriuretic effect has been ascribed to an inhibition of the inner medullary collecting duct cells Na^+/K^+ ATPase. In eight additional newborn rabbits, a bolus injection of 1 nmol · kg^{-1} of endothelin-1—a dose that usually induces marked renal and systemic vasoconstriction in adult models—did not affect systemic or renal hemodynamics. In conclusion, endothelin induces renal and systemic vasoconstriction, and affects water and sodium homeostasis during the neonatal period. However, these effects occur under higher doses than those used in adult animals. This age difference in systemic and renal responsiveness is probably mediated by receptor immaturity and/or interference of high levels of counteracting hormones present during the neonatal period.

11β-hydroxy-steroid dehydrogenase (11βOHSD) affects prednisolone/prednisone ratio in the kidney. *M. Conti, G. Delaloye, F.J. Frey, C.*

Marone, and B.M. Frey, Division of Nephrology, University of Berne, Switzerland, and Department of Medicine, Ospedale S. Giovanni, Bellinzona, Switzerland. 11βOHSD converts prednisolone (Po) into biologically inactive prednisone (P). One might predict that tissues with high activity of 11βOHSD exhibit a low Po/P concentration ratio and therefore a relatively low immunosuppressive effect and vice versa. In order to demonstrate the relevance of 11βOHSD for Po/P ratios, rats were injected with Po, and Po/P concentrations were measured by HPLC. The Po/P concentration ratio was about 25 to 50 times higher in liver than in kidney tissue, and severalfold higher (5- to 15-fold) in lung, heart, spleen or plasma than in kidney. The tissue distribution of mRNA of 11βOHSD parallels the Po/P ratios. Inhibition of 11βOHSD by glycyrrhetinic acid (GA) increased the ratio in the kidney tissue three- to 15-fold. In order to assess the impact of 11βOHSD on Po/P in humans, 10 healthy volunteers were given Po as a zero order infusion for 13 hours with and without GA. Po/P ratios in plasma and urine were measured. Plasma Po/P was unaffected by GA, however GA increased the urinary ratio in all subjects. Conclusion: Due to the high activity of 11βOHSD, local conversion of Po to inactive P occurs in the kidney at a much higher rate than in other tissues. Therefore, the inhibition of the local enzyme might be a strategy to selectively increase the immunosuppressive effect of prednisone therapy in the transplanted kidneys.

The myth of low bone mass in idiopathic calcium renal stone formers. *J.-P. Casez, Ch. Hug, B. Hess, K. Lippuner, D. Ackermann, and Ph. Jaeger, Policlinique Médicale Universitaire et Clinique Urologique, Hôpital de L'ile, Berne, Switzerland.* To assess bone mineral density (BMD) in calcium nephrolithiasis, dual energy X-ray absorptiometry was used at lumbar spine, upper femur (femoral neck, Ward's triangle and total area), tibial diaphysis, and tibial distal epiphysis. Results obtained in 99 male idiopathic calcium stone formers were compared with those of 234 healthy male controls. Patients were investigated on a free choice diet. Based on the mean of two measurements of 24-hour urinary excretion rate of calcium, patients were classified as normocalciuric or hypercalciuric calcium stone formers (≤0.1 mmol/kg/day and >0.1 mmol/kg/day, respectively). The calcium/creatinine concentration ratio was calculated out of the second (that is, fasting) morning urine. BMD was compared between calcium stone formers and controls as well as between hypercalciuric and normocalciuric stone formers using: (1) non-corrected BMD, (2) BMD corrected for age, height and BMI, and (3) a skeletal score based on a tercile distribution of BMD values at the following four sites: lumbar spine, Ward's triangle, tibial diaphysis, and tibial epiphysis. No significant difference was seen in corrected or non-corrected BMD at any site, be it in the whole group be it in both subgroups of stone formers, as compared with the control group. The skeletal score was significantly lower in calcium stone formers than in controls ($P = 0.04$). However, this difference was no longer significant after exclusion of 5 patients with accepted causes for secondary osteoporosis. There was a trend for a lower skeletal score in patients with versus those without history of a low calcium diet in the past, but no correlation could be found between BMD at any site and current calcium intake as well as with fasting calcium excretion or with 24-hour urinary excretion rate of calcium. We conclude that idiopathic calcium nephrolithiasis is generally not associated with low bone mass, although calcium restriction might lead to osteopenia in some patients.

Urea elimination during hemodialysis treatment with stable or variable dialysate sodium. *Marcel Auer, Willi Probst, and Ulrich Binswanger, Nephrologische Abteilung, Department Innere Medizin, Universitätsspital, Zürich, Switzerland.* Urea elimination during hemodialysis is greater at initiation of therapy due to a larger concentration gradient as compared to the situation at the end of treatment. The rapid decrease of the serum urea concentration can result in a disequilibrium syndrome. The present study was undertaken to compare the effect of constant versus changing sodium content of dialysate on urea extraction by sampling dialysate every 15 minutes. Six patients were studied each during a dialysis treatment with a stable dialysate sodium of 140 mmol/liter and with a sodium profile starting at 150 mmol/liter and reaching continuously 140 mmol/liter after 2.5 hours of treatment. The blood urea at start of the treatment was 20.9 ± 7.1 mmol/liter with stable sodium and 19.8 ± 6.6 mmol/liter with sodium profile (difference not significant). The results of the urea extraction (mmol) were as follows:

	Minutes			
	0–15	15–30	30–45	45–60
Na stable	49.3 ± 19.2	51.3 ± 19.0	46.7 ± 19.2	45.0 ± 17.5
Na profile	46.8 ± 18.2	47.8 ± 20.0	45.7 ± 19.5	42.1 ± 17.9
	Minutes			
	60–75	75–90	105–120	135–150
Na stable	43.5 ± 19.2	39.7 ± 15.4	33.5 ± 18.2	30.2 ± 14.8
Na profile	38.7 ± 17.5	36.7 ± 15.0	30.6 ± 13.4	27.3 ± 12.0

Differences for each 15 min. not significant (paired *t*-test)

The total amount of extracted urea was 408.3 ± 171.6 mmol during treatment with stable sodium, versus 378.9 ± 159.0 mmol during treatment with sodium profile (difference not significant). Our data show a tendency towards lower urea extraction rate and total amount during treatment with a sodium profile. This might contribute to the avoidance of a disequilibrium syndrome and to lower dialysis efficiency under these conditions.

Increase of endotoxin concentration due to bacterial contamination of the dialysate during dialysis. *D. Kiss, K. Donauer, and K. Gyr, Dialysestation, Medizinische Klinik, Kantonsspital Liestal, Switzerland.* The endotoxin concentration and the bacterial contamination of purified water and dialysate at the start and at the end of treatment were investigated. As a buffer acetate or bicarbonate was used. The endotoxin concentration was determined by a quantitative colorimetric assay. The bacterial contamination was determined in spot samples, by placing bacterial filters in the water and the dialysate pathway, respectively. The endotoxin concentration of treated water was 12.2 ± 4.5 pg/ml ($N = 26$). In the dialysate the endotoxin concentration was 25.8 ± 20.6 pg/ml at the start of the treatment. At the end of treatment the endotoxin concentration increased significantly to 52.6 ± 43.5 pg/ml. The increase of endotoxin concentration was significantly higher during bicarbonate dialysis (+35% vs. +67%). The bacterial contamination was positive in all samples performed. In spite of regular disinfection of the dialysis machine, there was a significant increase of endotoxin concentration during dialysis. During bicarbonate dialysis the increase of endotoxin concentration is significantly higher than during acetate dialysis. Bacterial growth within the dialysis machine might contribute to this phenomenon.

Peritonitis due to perforation of the distal ileum by a rosemary branch in a patient on continuous ambulatory peritoneal dialysis (CAPD). *A. Edward, E. Battaglia, E. Walder, and J.A. Cerutti, Reparto di Nefrologia, Ospedale Civico, Lugano, Switzerland.* A 63 year old, male, insulin dependent diabetic who has been treated for end-stage renal disease by CAPD for 40 months was admitted to our unit with cloudy dialysate but few other symptoms. The following comorbid conditions existed at the time of initiation of dialysis: severe progressive retinopathy, hypertension, peripheral neuropathy, gastroparesis, peripheral vascular disease, and ischemic heart disease. He complained of nausea and vomiting, had slight abdominal pain, and a temperature of 37.2°C. Acute peritonitis due to both gram-positive and gram-negative organisms was diagnosed and the appropriate antibiotic therapy was initiated. During the next few days the dialysate remained cloudy and the abdominal pain was localized to the right lower abdominal quadrant and became aggravated. Sonography, X-ray and barium enema examinations revealed normal findings. A laparoscopy was then performed revealing a fibrous layer with a thin foreign body protruding at the terminal ileum. This foreign body was then removed, and since there was no intestinal leakage, no suture was employed. This foreign body was identified as a rosemary stick 5.5 cm long. After the removal of the foreign body we were able to continue CAPD without interruption. All symptoms abated, dialysate remained clear with negative microbiology.

Incidence of *pneumocystis carini pneumonia* (PCP) after kidney allotransplantation (KA): When is prophylactic treatment needed? *Ann-Kathrin Schwarzkopf, Ruedi Speich, Gérald Keusch, and Ulrich Binswanger, Nephrologische Abteilung, Departement für Innere*

Medizin, Universitätsspital Zürich, Switzerland. An increasing rate of PCP after KA was observed starting in 1989. Until 1991, nine cases out of 205 allotransplantations were diagnosed. 80/205 patients (group I) received induction immunosuppression with ATG, prednisone (P) and azathioprine (A); ATG was switched to cyclosporin A (CsA) after seven to 10 days. 126/205 (group II) received triple immunosuppression with P, A, CsA immediately after kidney grafting. PCP occurred 36 to 117 days after transplantation in 7/80 and 2/126 patients, respectively (χ^2-test: $P < 0.05$). PCP disease related to rejection therapy with ongoing triple immunosuppression is outlined in the table. (Number of patients lost).

	PCP			
Rejection therapy	*N*	group I	group II	*N*
no rejection	26	1	—	49
P-pulses	37	2	1 (1)	40
P + ATG	1	—	—	24
P + OKT	16	4 (2)	—	4
P + ATG + OKT	—	—	1 (1)	8

P-pulses with and without induction therapy are associated with a low rate of PCP. Expanding the number of antirejection agents results in 4/17 and 1/36 incidences of PCP for group I and II, respectively (χ^2, P = NS). P-pulses followed by OKT3 treatment (plus ATG in one case) were associated with 5/28 PCP as opposed to 3/77 after P-pulses alone (χ^2, $P < 0.06$) and no disease after P + ATG. Three-fourths of the fatal cases occurred in patients with multiple infections, PCP being a contributing factor to the main cause of death. In conclusion, P-pulses followed by OKT3 rejection treatment include a risk for PCP, which might be reduced by prophylactic therapy.

Antilymphocytic globulins may promote the development of monoclonal gammopathy after renal transplantation. *J. Passweg, H.A. Bock, and G. Thiel. Abteilung Nephrologie, Kantonsspital Basel, Basel, Switzerland.* We retrospectively studied the incidence of monoclonal gammopathy in 436 renal transplant patients from this center transplanted between 1982 and 1991. Immunoelectrophoresis was performed at yearly intervals after transplantation in 318 of the 436 patients. There were 24 cases of clonal gammopathy: 18 were monoclonal, six were bi-, or triclonal. As in other gammopathy patients, there was a predominance of IgG and κ-light chain subtypes (IgG: 21, IgA: 1, IgM: 2, κ: 17, λ: 11). Gammopathy was transient in five patients. The five-year cumulative incidence of gammopathy was 8% by life-table analysis, much higher than in the same age group of the general population. None of the patients developed multiple myeloma during follow-up (median 2.5 years; range 0–9). Twenty-one are currently alive and well, and three died of unrelated causes. In one patient, gammopathy coincided with a non-Hodgkin's Lymphoma which was successfully treated by chemotherapy. The median age of patients with gammopathy was 52 (16–62) years at transplantation and was similar to patients without gammopathy [49 (9–71) years]. Eighteen of the 24 gammopathies appeared within the first two years after transplantation. The use of antilymphocytic antibodies in the initial immunosuppressive regimen conveyed a significantly increased risk of developing monoclonal gammopathy: 11 of 15 patients who developed gammopathy within the first two years after transplantation had received OKT3 or ATG, whereas only 81 of 235 first cadaveric transplants during the same time period had received this therapy ($P < 0.0005$). This may explain, why in 1989–1990, when antilymphocytic antibodies were more often used, we observed a remarkable increase ($P < 0.005$) of the two-year incidence of gammopathy (9/74), when compared to the years 1982–1988 (7/236). In conclusion, monoclonal gammopathy is an infrequent complication of renal transplantation. Immunosuppressive induction therapy with antilymphocytic substances may promote its development. Further follow-up of these patients is warranted to evaluate the dignity of this syndrome.

Prophylactic oral anticoagulation in nephrotic patients: A decision analysis. *F.P. Sarasin, and J.A. Schifferli, Division of Nephrology, University of Geneva Medical School, Geneva, Switzerland.* Thromboembolic episodes, including deep vein thrombosis in the legs (DVT), and renal vein thrombosis (RVT), remain one of the most serious complications of nephrotic syndrome. Once the diagnosis of acute thrombosis is established, oral anticoagulation therapy should be started immediately, but whether the high incidence of thromboembolic events justifies its prophylactic administration remains controversial. Using a Markov decision analysis model, explicitly considering the consequences of recurrent embolic and bleeding events, we compared a strategy of oral anticoagulant therapy (AC) started immediately after a first thromboembolic episode with a strategy of prophylactic oral anticoagulant therapy (ProphAC). From the literature, we estimated the rate of RVT to be 9%/year and of DVT to be 3%/year, and calculated the life expectancy (LE) and the number of fatal complications from embolic and major bleeding events for a hypothetical cohort of 10,000 fifty-year old patients with membranous glomerulopathy. If they remained nephrotic for two years, the analysis revealed:

Strategy	LE (years)	Fatal emboli	Fatal bleeding
AC	16.3	271	13
ProphAC	16.6	47	69

Excluding patients with diabetic nephropathy, the overall number of fatal emboli prevented by the ProphAC strategy exceeded the one of fatal bleeding events for all clinically meaningful ranges of the following parameters: age, nephrotic syndrome duration, DVT and RVT rates, likelihood of embolization, and mortality rates of embolic and bleeding events. We conclude that in the clinical setting of nephrotic syndrome, the benefits provided by prophylactic oral anticoagulation outweigh its risks because of the extremely high rate of thromboembolic episodes.

Use of sandimmune (SIM) in idiopathic nephrotic syndrome. *B. von Graffenried, Klinische Forschung, Sandoz Pharma AG, Basel, Switzerland.* Three hundred forty-one patients were treated with SIM with the aim of inducing remission. One hundred forty-six had minimal change nephropathy (MCN), and 195 had focal segmental glomerulosclerosis (FSGS); 104 were steroid-dependent (SD, 82 were MCN) and 226 were steroid-resistant (SR, 163 were FSGS); steroid status was unknown for 11. Mean SIM doses were 4.7 mg/kg/day in the 213 adults and 6.0 mg/kg/d in the 128 children. In SD patients, complete remissions (CR) were achieved in 80%, and partial remissions (PR) in 10%. In SR patients treated with SIM alone, CR occurred in 14% and PR in 25%, significantly more than in untreated controls. In SR patients treated with SIM + low dose prednisone, responder rates were higher (CR 25%, PR 33%). Median time until remission was one month in MCN and two months in FSGS. There was no correlation between SIM blood trough levels and efficacy. Complete remission was maintained for six months in 76% if SIM was continued, but in only 20% six months after stopping therapy. In a further 134 SD patients SIM was used to maintain steroid-induced remissions. This was possible in 87% despite withdrawal of steroids. In two randomized studies, SIM was as effective as chlorambucil and cyclophosphamide, but relapses occurred faster after withdrawal of SIM. Catch-up growth was observed in children upon steroid withdrawal. SIM was discontinued because of adverse events in 7.6%, mostly because of renal dysfunction. In most cases, these patients already had abnormal renal function at baseline and were treatment failures. In renal biopsies, moderate interstitial fibrosis without arteriolopathy was seen in 3/34 patients with MCN. In 2/12 patients with FSGS, SIM-nephropathy was suspected. The most frequent adverse events were hypertrichosis, gingival hyperplasia, gastrointestinal complaints, and hypertension. SIM can be recommended in steroid-resistant NS and in steroid-dependent forms failing on cytostatic agents.

Effects of calcium salts and different calcium (Ca) dialysate concentrations on the mineral metabolism of hemodialysis (HD) patients. *C. Zehnder, M. Kränzlin, and R. Kizhakekkara, Division of Nephrology, Kantonsspital, Aarau, Switzerland.* Ca salts for the control of hyperphosphatemia in dialysis patients are now widely used; unfortunately, they may cause hypercalcemia. To avoid this complication, dialysates (D) with reduced Ca concentrations are increasingly recommended. In this prospective study we analyzed the effect of Ca salts and different Ca D concentrations on the mineral metabolism of 12 HD patients. The

study was divided into four three month periods according to the D Ca: I standard 1.75; II 1.25; III 1.5; IV 1.75 mmol/liter. Ca salts [11 patients Ca acetate (Ca ac), 1 patient Ca ketoglutarate] were adjusted in order to achieve normal serum phosphate (sPO_4) concentrations. At baseline and at the end of each period serum Ca (sCa), sPO_4, alkaline phosphatase (aP), intact parathormone (iPTH), osteocalcin (OC) and 1,25 dihydroxy vitamin D_3 ($1,25(OH)_2D_3$) were measured. At baseline three patients had high iPTH (320.8 ng/ml) and were analyzed separately. Three patients were transplanted after seven months. Results were as follows (means):

	Ca dose *mmol/ day*	sCa *mmol /liter*	sPO_4 *mmol/ liter*	aP *IU/ liter*	iPTH *ng/ml*	OC *ng/ml*	$1,25(OH)_2D_3$ *pmol/liter*
baseline	23.3	2.61	2.06	117.4	30.0	16.4	18.5
I Ca 1.75	21.7	2.62	1.96	98.4	22.4	17.8	15.8
II Ca 1.25	25.0	2.38[a]	2.39[b]	120.2	61.3[b]	23.2	11.2
III Ca 1.50	25.4	2.46	2.08	88.7	38.3	19.5	9.7
IV Ca 1.75	22.5	2.71	1.78	89.8	29.5	18.7	11.3

[a] $P < 0.001$, [b] $P < 0.01$

3/9 patients became hypercalcemic in I and 3/6 in IV. 4/9 patients developed elevated concentrations of iPTH with D Ca 1.25 mmol/liter. $1,25(OH)_2D_3$ was generally very low. In the three patients with hyperparathyreoidism iPTH remained unchanged (398.6, 435.9, 354.0 and 399.0 ng/ml in I through IV). Conclusions: In our HD patients with normal iPTH, the reduction of Ca D to 1.25 mmol/liter led to lower sCa concentrations with compensatory hyperphosphatemia and to stimulation of PTH secretion (and possibly increasing bone turnover with rising trend of OC) in spite of a daily Ca dose of 25 mmol (4 g) Ca ac. Lowering of D Ca should be done with caution.

Effect of combined pancreas-kidney transplantation on fasting and postprandial lipid levels. *H. Drexel, J.A. Bleisch, G. Kuster, J. Záruba, F.W. Amann, and U. Binswanger, Departement Innere Medizin, Universitätsspital Zürich, Switzerland.* Although fasting lipid levels of patients with insulin-dependent diabetes mellitus (IDDM) improve after combined pancreas-kidney transplantation, the incidence of atherosclerotic complications in these patients remains increased. In search for other possible atherogenic factors, parameters of postprandial lipid transport were studied in eight IDDM patients with a kidney graft (KD) and seven with a combined pancreas-kidney graft (PK), and compared to those of eight non-diabetic kidney graft recipients (controls, K). Six hours after a standardized vitamin A-enriched fatty meal, postprandial plasma levels of chylomicrons and chylomicron remnants were quantitated by measuring retinyl palmitate concentrations in density fractions >1.006 and <1.006 g/ml. Also, fasting and postprandial plasma levels of triglycerides, cholesterol, HDL cholesterol, HDL_2 cholesterol, HDL_3 cholesterol, apolipoproteins A-1 and B, insulin and C-peptide were measured by routine methods. Postprandial chylomicron remnant-associated retinyl palmitate was significantly elevated in the PK group as compared to the KD and K groups (mean ± SD 2796 ± 1037 vs. 1221 ± 610 ng/ml, $P = 0.0038$; and 2796 ± 1037 vs. 1500 ± 721 ng/ml, $P = 0.0151$), respectively. In comparison with group K, group PK had lower fasting and postprandial levels of triglycerides (1.04 ± 0.27 vs. 2.11 ± 0.74 mmol/liter at 0 hours, $P = 0.0078$; and 1.56 ± 0.44 vs. 2.89 ± 1.35 mmol/liter at 6 hours, $P = 0.0206$), and Apo B (0.98 ± 0.16 vs. 1.54 ± 0.61 g/l at 0 hours, $P = 0.0055$; and 1.01 ± 0.19 vs. 1.56 ± 0.59 g/liter at 6 hours, $P = 0.0151$). We conclude that IDDM patients with a functioning pancreas graft exhibit an important defect of postprandial chylomicron remnant clearance. Because remnant particles are atherogenic, this defect may predispose pancreas graft recipients to atherosclerotic complications in spite of their favorable fasting lipid profile.

Immunoprophylaxis against CMV in seronegative recipients of kidney allografts from seropositive donors. *Stefan Mariacher, Ruedi Speich, Gérald Keusch, John D. Auracher, Werner Wunderli, Reinhard Zbinden, Felix Largiadèr, and Ulrich Binswanger, Universitätsspital Zürich, Switzerland.* High risk patients were analyzed during a period with immunoprophylaxis (Cytotect, 4 mg/kg body wt; day 0, 2, 4, 14, 28) from 1.1.89 to 31.10.91 and compared to patients without this treatment observed from 1.1.84 to 31.12.88. Results were as follows:

Serological and disease state	with IP $N = 12$	without IP $N = 26$
Seroconversion	8/12	19/26
asymptomatic	2/8	2/19
CMV disease	6/8	17/19
moderate	4/6	11/17
severe	2/6	6/17
death	0/8	3/19
Clinical signs		
fever	5/6	16/17
leukopenia	2/6	14/17
thrombopenia	2/6	6/17
hepatitis	—	13/17
pneumonitis	2/6	6/17
pericarditis	—	2/17
myocarditis	—	1/17
encephalitis	—	5/17
renal failure	—	5/17

Frequency of seroconversion and disease was not altered by immunoprophylaxis; however, severity of disease and number of organs involved are aggravated and higher without prophylactic treatment.

A randomized prospective trial of prophylactic immunosuppression with OKT3 versus ATG-Fresenius (ATG-F) after renal transplantation. *H.A. Bock, R. Zürcher, M. Mihatsch, J. Landmann, and G. Thiel, Abteilung Nephrologie und Organtransplantation, Kantonsspital Basel, Basel, Switzerland.* We carried out a randomized prospective trial in 104 consecutive renal transplant recipients to compare prophylactic administration of monoclonal OKT3 (5 mg/day for 7 days from day 0) with polyclonal rabbit ATG-F (4 mg/kg/d for 7 days from day 0). Concomitant immunosuppression included azathioprin and steroids from day 0 and cyclosporin A from day 4. Target parameters were one-year graft and patient survival, rejection and infection rates and graft function. The present data include six-month follow-up in all patients and one-year follow-up in 73%. The study groups ($N = 52$ each) were well matched for all relevant parameters. Four patients in the OKT3 group and one patient in the ATG-F group died, all due to severe infection. Seven additional grafts in the OKT3 group and three in the ATG-F group were lost, mainly (6 and 2, respectively) due to vascular rejection. No lymphomas were observed.

		OKT3	ATG-F	*P*
1-yr survival	Patient	92%	98%	NS
(Kaplan-Meier)	Graft	78%	92%	<0.05
Rejections/patient	"Clinical"	1.00 ± 0.16	0.75 ± 0.14	NS
Mean ± SEM	Biopsy-proven	0.52 ± 0.10	0.31 ± 0.09	NS
Infections/patient	Severe	0.90 ± 0.22	0.63 ± 0.15	NS
Mean ± SEM	Minor	2.19 ± 0.24	1.33 ± 0.16	<0.05
1-yr creatinine	μmol/liter	137 ± 9	139 ± 15	NS
Side effects	T > 37.5°C	41/52	8/52	<0.001
1st week				
Other: headache, dyspnea, pulm. edema, GI tract		23/52	5/52	<0.001

The high incidence of side effects in the OKT3 group occurred despite prophylactic steroids (1 g MP i.v. one to four hours before OKT3 or ATG-F). OKT3 patients were less likely to survive the first year without biopsy-proven rejection (58% vs. 76%, $P < 0.05$). In conclusion, prophylactic administration of OKT3 does not improve outcome or diminish immunological graft loss when compared to ATG-F, but

conveys an increased rate of infections and side effects. For prophylactic immunosuppression after renal transplantation, ATG-F appears to be preferable over OKT3.

Excellent uricosuric efficacy of benzbromarone in cyclosporin A treated renal transplant patients: A prospective study. *R.M. Zürcher, H.A. Bock, and G. Thiel, Abteilung für Nephrologie, Kantonsspital Basel, Basel, Switzerland.* Patients on cyclosporin A (CsA) often develop hyperuricemia and gout. Since allopurinol may be undesirable because of its interaction with azathioprine, we prospectively studied the uricosuric efficacy of benzbromarone (Bbr; Desuric®) in hyperuricemic patients on CsA. Seventeen CsA-treated renal transplant patients with stable graft function and hyperuricemia (>359 μmol/liter for females, >491 μmol/liter for males) were given 100 mg of benzbromarone daily for four weeks in addition to their established medication.

	before Bbr	1 week Bbr	4 weeks Bbr
Creatinine clearance *ml/min*	48.6 ± 4.6		44.1 ± 3.8
Plasma uric acid *μmol/l*	570 ± 22	296 ± 26[b]	320 ± 28[b]
Fractional uric acid clearance %	5.8 ± 0.5		16.6 ± 1.2[b]
Urinary uric acid excretion *μmol/24 hr*	2212 ± 231		3077 ± 293[a]

Data are given as mean ± SEM; [a] $P < 0.01$; [b] $P < 0.001$

Benzbromarone normalized plasma uric acid in 15 of 17 patients. The remaining two patients had creatinine clearances of 23 and 25 ml/min, the lowest of the entire study group. The relative increase of fractional uric acid clearance closely correlated with baseline creatinine clearance ($r = 0.64$, $P < 0.005$). None of the patients experienced any side effects. There were no changes in electrolytes, liver enzymes or hematologic parameters. In conclusion, benzbromarone normalized serum uric acid in all CsA-treated renal transplant recipients with creatinine clearance >25 ml/min. The increase in renal uric acid excretion probably reflects diminished extrarenal uric acid elimination, which is expected to occur as plasma uric acid is normalized. Due to its lack of significant side effects, benzbromarone appears to be preferable to allopurinol in CsA treated renal transplant recipients with a creatinine clearance above 25 ml/min.

Post-transplant renal bone disease. *V. Briner, G. Thiel, M.C. Faugere, B. Bognar, J. Landmann, V. Kamber, and H. Malluche, Division of Nephrology, Basel, Switzerland and Lexington, Kentucky, USA.* After renal transplantation (RT) and restoration of glomerular filtration and production of $1,25(OH)_2D_3$, renal osteodystrophy (OD) is expected to resolve. However, patients receiving azathioprine (AZA) and prednisone (P) develop osteopenia. The present study prospectively investigates serum parameters of bone metabolism and histologic changes of bone in patients on cyclosporin A (CsA) with low or no maintenance P dose over a two year period. After RT in 34 patients (age: 18 to 67 years) immunosuppressive therapy (IST) was initiated with CsA (5 mg/kg body wt), AZA (2 mg/kg) and P (0.5 mg/kg). AZA was discontinued after two months and P tapered. To suppress rejection 18 patients required maintenance P therapy. After RT high PTH and osteocalcin (Gla) decreased while $1,25(OH)_2D_3$ increased significantly. Alkaline phosphatase increased transiently after RT. At RT bone histology revealed mixed uremic OD in 63%, adynamic bone disease in 33.5%, low turnover osteomalacia in 4% of patients. There was a positive relationship between PTH and Gla and histologic parameters of bone formation and resorption ($P < 0.01$). In 85.4% of biopsies there was aluminum staining which decreased after RT. Patients with initial biopsy of mixed OD tended to decrease while patients with initial biopsies with adynamic OD tended to increase bone turnover within one year after RT. Bone volume did not change after RT. Conclusion: With the present regimen of IST pre-existing renal OD improves after successful RT without loss of bone volume.

Outcome after renal transplantation of patients with diabetic nephropathy and of patients older than 60 years of age. *A. Fischer, and M. Leski, Département de Médecine, Hôpital Cantonal Universitaire de Genève, Genève, Switzerland.* We reviewed the experience of a small transplantation center (20 to 30 renal transplantations a year) for patients considered at increased risk for this procedure. Between September 1983 (introduction of cyclosporine) and April 1992, 198 kidney allografts (almost exclusively from cadaveric donors) were performed, of which 163 were followed at our institution. We retrospectively compared the outcome of the allografts transplanted into patients with diabetic nephropathy ($N = 23$), and into patients older than age 60 ($N = 26$), with those transplanted into patients with neither risk factor ($N = 114$). One and three years graft survivals were, respectively: 83% and 78%; 92% and 82%; 87% and 79%. One and three years patient survivals were respectively: 90% and 90%; 96% and 91%; 97% and 97%. Morbidity, as assessed by the number of days spent in the hospital after the procedure, was increased for the diabetic population. Patients older than 60 years of age developed less rejection episodes in the first three months after transplantation. Our results favorably compare with those of larger series in the literature. Although this study lacks statistical power because of the small number of cases, it interestingly shows no difference in outcome between the groups at increased risk and the group without these risk factors. This may partly be explained by a low incidence of cardiovascular complications in the patients considered at increased risk, due to a careful selection.